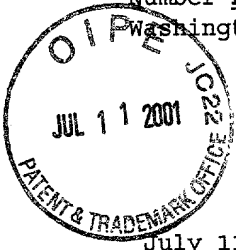


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July 11, 2001
Date

Denise Ortega
Name

Denise Ortega
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jan Zavada et al.

Serial No.: 09/772,719

Group Art Unit:

Filed : January 30, 2001

Examiner:

For : MN Gene and Protein

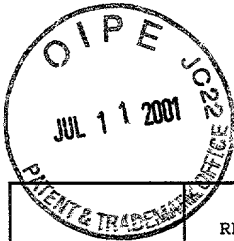
AMENDMENT TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is a Preliminary Amendment and Request for Declaration of an Interference with U.S. Patent No. 6,087,098.

The fee for claims has been calculated as shown below:



	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE
TOTAL	30	MINUS	20	10	X \$ 18	\$180.00
INDEP.	3	MINUS	3	= 0	X \$ 80	\$ 0.00

[] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM + \$270 \$

TOTAL \$180.00

A request for payment by credit card of the fee of the additional claim fee accompanies this transmittal. If for any reason, the credit card payment is not adequate for payment of any fees or should any additional fees be determined to be necessary in connection with this paper, Applicants respectfully request that any such fees be charged to Deposit Account No. 12-0615.

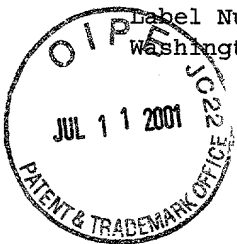
Respectfully submitted,

Leona L. Lauder
Attorney for Applicants
Registration No. 30,863

Dated: July 11, 2001

#3

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Denise Ortega

Name

July 11, 2001

Date

Signature

Denise Ortega

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jan Zavada et al.

Serial No.: 09/772,719

Group Art Unit:

Filed : January 30, 2001

Examiner:

For : MN Gene and Protein

PRELIMINARY AMENDMENT AND REQUEST
FOR DECLARATION OF AN INTERFERENCE WITH
U.S. PATENT NO. 6,087,098

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully request that an interference be declared between their above-identified application and U.S. Patent No. 6,087,098 (issued July 11, 2000; hereinafter cited as "the McKiernan et al. '098 patent"; copy enclosed as Exhibit 1). Applicants further respectfully request that the Applicants be designated as the senior party in said interference, since their

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above-identified application has effective filing dates of March 11, 1992, October 21, 1992, December 30, 1993, June 15, 1994 and June 7, 1995, whereas the only priority date claimed for the McKiernan et al. '098 patent is April 15, 1997. The earliest effective filing dates for the instant application are about five (5) years earlier than the priority date for the McKiernan et al. '098 patent, and the latest claimed priority date is about two years earlier than the priority date for the McKiernan et al. '098 patent. Further, the PCT application corresponding to the parent application of which the instant application is a continuation -- Zavada et al., WO 95/34650 -- was published on December 21, 1995.

Applicants respectfully request that the instant application be amended as indicated below before the requested interference is declared, and before examination of the claimed invention is made.

IN THE SPECIFICATION

Please make the amendments to the Specification as indicated below:

Please replace the paragraph on page 1, lines 2-14 with the following paragraph:

This application is a continuation of U.S. Serial No. 08/485,049 (filed June 7, 1995), which issued as U.S. Patent 6,204,370 on March 20, 2001, which is a continuation-in-part of now pending U.S. Serial No. 08/260,190 (filed June 15, 1994), which, in turn, is a continuation-in-part of U.S. Serial No. 08/177,093 (filed December 30, 1993), which issued as U.S. Patent 6,051,226 on April 18, 2000, which is, in turn, a continuation-in-part of U.S. Serial No. 07/964,589 (filed October 21, 1992), which issued as U.S. Patent No. 5,387,676 on February 7, 1995. This application declares priority under 35 USC § 120 from those U.S. applications, and also under 35 USC § 119 from the now pending Czechoslovakian patent application PV-709-92 (filed March 11, 1992).

IN THE CLAIMS

Please cancel Claims 1, 2, 6, 13-17, 24, 25 and 35-37. Please insert the following new Claims 38-67.

38. A method for diagnosing renal carcinoma in a human subject which comprises:

(a) obtaining mRNA from a sample of the subject's blood;

(b) preparing cDNA from the mRNA from step (a);

(c) amplifying DNA encoding MN present in the cDNA prepared in step (b); and

(d) detecting the presence of any resulting amplified DNA, the presence of such amplified DNA being diagnostic for renal carcinoma.

39. The method of claim 38, wherein in step (c) amplification of DNA encoding MN is effected by a polymerase chain reaction utilizing at least two oligonucleotide primers.

40. The method of claim 39, wherein each of the primers is capable of specifically hybridizing with DNA encoding MN.

41. The method of claim 39, wherein the primers comprise oligonucleotides that are effective to amplify a segment of the MN cDNA.

42. The method of claim 41 wherein said MN cDNA has the nucleotide sequence of SEQ ID NO: 1.

43. The method of claim 42 wherein one of said primers comprises the nucleotide sequence of nucleotide 404 to nucleotide

423 of Figure 1A-1B and of SEQ ID NO: 1, and the other primer is complementary to nucleotides 789 to 770 of Figure 1A-1B and of SEQ ID NO: 1.

44. The method of claim 38, wherein the presence of any amplified DNA in step (d) is detected using a labeled MN nucleic acid probe which specifically hybridizes with MN nucleic acids encoding a MN protein or MN polypeptide, which MN protein or MN polypeptide has an amino acid sequence of or from SEQ ID NO: 2.

45. The method of claim 44, wherein the labeled probe is radiolabeled.

46. The method of claim 39 wherein each of said primers is an isolated and purified MN nucleic acid, which has a length of from 16 nucleotides to 50 nucleotides, and comprises a nucleotide sequence which is selected from the group consisting of: nucleotide sequences that specifically hybridize to SEQ ID NO: 1 or to the complement of SEQ ID NO: 1; and

wherein an appropriate pair of primers is selected for effective amplification.

47. The method of claim 46 wherein said nucleotide sequence specifically hybridizes to a MN nucleotide sequence contained in any of the plasmids A4a, XE1 and XE3, which were deposited at the American Type Culture Collection in the United States of America under the respective ATCC Nos. 97199, 97200 and 97198.

48. A method of screening for preneoplastic/neoplastic disease associated with abnormal MN gene expression comprising:

(a) determining whether abnormal MN gene expression is present in a vertebrate using a nucleic acid based assay on a sample from said vertebrate; and

(b) if abnormal MN gene expression is determined to be present in said vertebrate, determining that said vertebrate has a significant risk of having preneoplastic/neoplastic disease;

wherein said MN gene encodes an MN protein that is encoded by a nucleic acid having a nucleotide sequence selected from the group consisting of:

(a) SEQ ID NO: 1;

(b) nucleotide sequences that hybridize under stringent conditions to complement of SEQ ID NO: 1; and

(c) nucleotide sequences that differ from SEQ ID NO: 1 or from the nucleotide sequences of (b) in codon sequence due to the degeneracy of the genetic code.

49. The method of claim 48 wherein said MN protein is encoded by SEQ ID NO: 1.

50. The method of claim 49 wherein said vertebrate is a mammal.

51. The method of claim 49 wherein said vertebrate is a human.

52. The method of claim 51 wherein said nucleic acid based assay is a polymerase chain reaction based assay.

53. The method of claim 51 wherein detecting abnormal MN gene expression comprises:

(a) obtaining mRNA from said sample from said human;
and

(b) detecting the presence of mRNA that is complementary to MN cDNA in the mRNA obtained from step (b), or

quantitating any mRNA that is complementary to MN cDNA in the mRNA obtained from step (b);

wherein the presence of mRNA complementary to MN cDNA in said mRNA obtained in step (a), or an abnormal level of mRNA complementary to MN cDNA in said mRNA obtained in step (a), indicates the presence of preneoplastic/neoplastic disease in said human.

54. The method of claim 51 wherein abnormal MN gene expression is detected by:

- (a) obtaining mRNA from a sample from said human;
- (b) preparing cDNA from the mRNA from step (a);
- (c) amplifying any DNA encoding a MN protein or a MN polypeptide that is present in the cDNA prepared in step (b); and
- (d) detecting the presence of any resulting amplified DNA, or quantitating any resulting amplified DNA, wherein the presence of such amplified DNA or an abnormal level of said amplified DNA indicates the presence of preneoplastic/neoplastic disease in said human.

55. The method of claim 54, wherein the step (c) amplification of DNA is effected by a polymerase chain reaction utilizing at least two oligonucleotide primers.

56. The method of claim 55 wherein each of the primers is capable of specifically hybridizing with DNA that encodes MN protein.

57. The method of claim 56 wherein said DNA that encodes MN protein has the nucleotide sequence of SEQ ID NO: 1.

58. The method of claim 57 wherein one of said primers has the nucleotide sequence of nucleotide 404 to nucleotide 423 of Figure 1A-1B or of SEQ ID NO: 1, and the other primer is complementary to nucleotide 789 to nucleotide 770 of Figure 1A-1B or of SEQ ID NO: 1.

59. The method of claim 54, wherein the presence of any amplified DNA in step (d) is detected using a labeled MN nucleic acid probe which specifically hybridizes with any amplified MN DNA.

60. The method of claim 59, wherein the labeled probe is radiolabeled.

61. The method of claim 60 wherein the labeled probe is radiolabeled with ³²P.

62. The method of claim 53 wherein said sample is selected from the group consisting of tissue sections, tissue extracts, tissue smears, whole cells, cell lysates, exfoliated cells, cell extracts, and body fluids.

63. The method according to claim 62 wherein said body fluid is selected from the group consisting of blood, serum, plasma, urine, semen, breast exudate, saliva, sputum, tears, mucous, fecal suspensions, gastric secretions, bile, lymph, cytosols, ascites, pleural effusions, amniotic fluid, bladder washes, bronchioalveolar lavages and cerebrospinal fluid.

64. The method according to claim 63 wherein said body fluid is selected from the group consisting of blood, serum and plasma.

65. The method according to claim 64 wherein said body fluid is blood.

66. The method of claim 54 wherein said preneoplastic/neoplastic disease associated with abnormal MN gene expression is selected from the group consisting of mammary, urinary tract, bladder, kidney, ovarian, uterine, cervical,

endometrial, squamous cell, adenosquamous cell, vaginal, vulval, prostate, liver, lung, skin, thyroid, pancreatic, testicular, brain, head and neck, mesodermal, sarcomal, stomach, spleen, gastrointestinal, esophageal, and colon preneoplastic/neoplastic diseases.

67. The method of claim 66 wherein said neoplastic disease is renal carcinoma.

REMARKS

The Specification has been amended to up-date the status of a claimed priority application which has been issued as a patent.

Claims 1, 2, 6, 13-17, 24, 25 and 35-37 were cancelled, and new claims 38-67 were added to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention, and to serve to provoke an interference with the McKiernan et al. '098 patent. Applicants respectfully submit that the new claims are supported throughout the application.

Appendices 2 and 3

To assist in the examination of this application and as required by 37 CFR 1.121, enclosed herewith as Appendix 2 is a marked-up version of the amendments specification. The modifications are indicated by underlining and in bold type for additions, and by strikeouts for deletions. Also enclosed as Appendix 3 is a clean set of all the claims now pending in accordance with 35 CFR 1.121(c)(3).

Proposed Count, and Question: How Does One Differentiate Clear Cell Renal Carcinoma with mRNA from Nucleated Cells from a Person's Blood Sample from Other Carcinomas Associated with MN Overexpression?

Claims 38-41 and 43-45 were substantially copied from claims 1-6 of the McKiernan et al. '098 patent to provoke an interference. Further, claims 54-61 are modified versions of claims 1-6 of the McKiernan et al. '098 patent. Applicants have respectfully supplied such modifications in that they question how one of skill in the art without a specific marker for a renal cell carcinoma cell, using a blood sample of a subject, could determine which of the wide variety of cancers associated with MN gene overexpression was being diagnosed?

Preneoplastic and/or neoplastic tumor cells over-expressing MN mRNA and MN protein, are overexpressing the same

mRNA whether in cervical tumor cells or in lung tumor cells or in renal carcinoma cells. Therefore, Applicants respectfully propose that the count for the interference be new claim 48 or claim 48 modified by appropriate dependent claims, such as, claims 49, 51 and 54. The claims of the instant application would read on such proposed counts. Further, claims 1-6 of the McKiernan et al. '098 patent would be encompassed by such proposed counts.

Support for New Claims 38-67

Detailed support in the instant specification for the claims based upon claims 1-6 of the McKiernan et al. '098 patent can be found in the claim chart of the accompanying Appendix 1. In that chart, support for each element of the McKiernan et al. claims 1-6 are shown both in the priority Zavada et al. U.S. Patent No. 5,387,676 ("the Zavada et al. '676 patent") (filed Oct. 21, 1992) [Exhibit 2], and in the parent to the instant application, Zavada et al. U.S. Patent No. 6,204,370 ("the Zavada et al. '370 patent") (filed June 7, 1995) [Exhibit 3]. The instant application is a continuation of the Zavada et al. '370 patent.

Support for the claims copied and modified from claims 1-6 of the McKiernan et al. '098 patent and for the other new claims, i.e., claims 42, 46-53 and 62-67 can be found in the

Zavada et al. '676 patent (filed Oct. 21, 1992), the great-great grand-parent application to the instant application, at least at col. 2, lines 20-50, at col. 3, lines 18-36, at col. 8, line 21 - col. 9, line 43, at col. 10, lines 45-50, at col. 11, lines 41-49, at col. 17, lines 3-29 and lines 44-60, at col. 17, line 67 to col. 18, line 34, at col. 20, lines 18-22, at col. 26, lines 5-16, at col. 35, line 58 to col. 36, line 21 [Example 12], at col. 44, lines 40-49 [Claim 8].

Further support for new claims 38-67 can be found in the parent application, the Zavada et al. '370 patent (filed June 7, 1995) at least at col. 1, lines 29-30, at col. 2, lines 17-32, at col. 3, lines 55-66, at col. 4, lines 20-48, at col. 10, lines 34-39, at col. 10, line 63 to col. 11, line 3, at col. 11, lines 54-61 (Figure 16), at col. 15, lines 41-52, at col. 16, lines 28-50, at col. 17, lines 3-7, at col. 17, lines 42-46, at col. 18, lines 55-60, at col. 18, lines 66-67, at col. 19, lines 19-23, at col. 27, line 41 to col. 28, line 2, at col. 33, line 30 to col. 34, line 13, at col. 33, lines 52-57 in combination with col. 34, line 58 to col. 35, line 6, at col. 57, lines 7-8, at col. 53, lines 19-49 (Example 11), at col. 57, lines 25-50 (Table 3), and at col. 127, lines 18-20 (Claim 2) and lines 47-48 (Claim 11).

Exemplary Quotes From the Zavada et al. '676 Patent [Exhibit 2] (filed Oct. 21, 1992)

Exemplary quotes from the Zavada et al. '676 patent [Exhibit 2] (filed Oct. 21, 1992) that highlight the support therein for the new claims 38-67 follow. For example, the Zavada et al. '676 patent [Exhibit 2] (filed October 21, 1992) states (at column 2, lines 20-36):

This invention is directed to said MN gene, fragments thereof and the related cDNA which are useful, for example, as follows: 1) to produce MN proteins/ polypeptides by biochemical engineering; 2) to prepare nucleic acid probes to test for the presence of the MN gene in cells of a subject: 3) to prepare appropriate polymerase chain reaction (PCR) primers for use, for example, in PCR-based assays or to produce nucleic acid probes; 4) to identify MN proteins and polypeptides as well as homologs or near homologs thereto; 5) to identify various mRNAs transcribed from MN genes in various tissues and cell lines, preferably human; and 6) to identify mutations in MN genes. The invention further concerns purified and isolated DNA molecules comprising the MN gene or fragments, thereof, or the related cDNA or fragments thereof.

[Emphasis added.] The Zavada et al. '676 patent then points to PCR-based assays and the identification of MN mRNA transcribed from cells of various tissues and cell lines, particularly of human origin, as aspects of this invention.

Body Fluids and Blood Sample. The Zavada et al. '676 patent at column 16, line 16 to column 17, line 29 describes

"Nucleic Acid Probes and Test Kits," and at column 17, lines 24-29 states:

Said probes thus can be useful diagnostically/prognostically. Said probes can be embodied in test kits, preferably with appropriate means to enable said probes when hybridized to an appropriate MN gene or MN mRNA target to be visualized. Such samples include tissue specimens, body fluids and tissue and cell extracts.

[Emphasis added.] The important point to be gathered from that quote is that the Applicants informed ones of skill in the art that they would be able to find MN mRNA in body fluids, such as, blood, from which the mRNA could be extracted from preneoplastic/neoplastic cells therein.

The Zavada et al. '676 patent then states at col. 3, lines 1-32:

The discovery of the MN gene and protein and thus, of substantially complementary MN genes and proteins encoded thereby, led to the finding that the expression of MN proteins was associated with tumorigenicity. That finding resulted in the creation of methods that are diagnostic/prognostic for cancer and precancerous conditions. . . .

MN proteins and genes are of use in research concerning the molecular mechanisms of oncogenesis, in cancer diagnostics/prognostics, and may be of use in cancer immunotherapy.

The present invention is useful for detecting a wide variety of neoplastic and/or pre-neoplastic diseases. Exemplary

neoplastic diseases include carcinomas, such as mammary, bladder, ovarian, uterine, cervical, endometrial, squamous cell and adenosquamous carcinomas; and head and neck cancers; mesodermal tumors, such as neuroblastomas and retinoblastomas; sarcomas, such as osteosarcomas and Ewing's sarcoma; and melanomas. Of particular interest are head and neck cancers, gynecologic cancers including ovarian, cervical, vaginal, endometrial and vulval cancers; gastrointestinal cancer, such as, stomach, colon and esophageal cancers; urinary tract cancer, such as, bladder and kidney cancers; skin cancer; liver cancer; prostate cancer; lung cancer; and breast cancer.

[Emphasis added.]

Reverse transcription is exemplified in the Zavada et al. '676 patent at least at col. 11, lines 41-49 where it is stated:

To find the MN gene, a lambda gt11 cDNA library from MX-infected HeLa cells was prepared. Total RNA from MX-infected HeLa cells was isolated by a guanidinium-thiocyanate-CsCl method, and the mRNA was affinity separated on oligo dT-cellulose. The synthesis of the cDNA and its cloning into lambda gt11 was carried out using kits from Amersham, except that the EcoRI-NotI adaptor was from Stratagene [La Jolla, CA (USA)].

At col. 20, lines 18-23, the Zavada et al. '676 patent refers to

Suitable detection means include the use of labels such as radionuclides, enzymes, coenzymes, fluorescers, chemilumescers,

chromogens, enzyme substrates or co-factors, enzyme inhibitors, free radicals, particles, dyes and the like.

[Emphasis added.]

The Zavada et al. '676 patent states, for example, at column 5, lines 13-16: "Preferred test kits comprise means for detecting or measuring the hybridization of said probes to the MN gene or to the mRNA product of the MN gene, such as a visualizing means." [Emphasis added.]

Claim 8. Claim 8 of the Zavada et al. '676 patent reads:

The isolated nucleic acid according to claim 1 wherein fragments of said nucleic acid are polymerase chain reaction primers for segments of MN genes wherein said primers specifically hybridize under stringent conditions to nucleic acid sequences encoding MN proteins or to sequences complementary to those encoding MN proteins, but do not hybridize under stringent conditions to nucleic acid sequences encoding carbonic anhydrase proteins or to sequences complementary to those encoding carbonic anhydrase proteins.¹

[Emphasis added.]

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1. The language in claim 8 referring to "carbonic anhydrase proteins" is an artifact of the patent prosecution process. The Zavada et al. '676 patent issued on February 7, 1995. After its issuance, MN was found to be a carbonic anhydrase isoenzyme and is now known as MN/CAIX or MN/CA9. In light of that fact, claim 8 has to be read for common sense reasoning as referring to the MN primers not hybridizing with other carbonic anhydrase isoenzymes.

Exemplary Quotes from the Zavada et al. '370 Patent [Exhibit 2] (filed June 7, 1995)

The Zavada et al., U.S. Patent No. 6,204,370 [Exhibit 3] (filed June 7, 1995) ("the Zavada et al. '370 patent"), the parent to the instant application, provides the same support as set forth above for the Zavada et al. '676 patent. However, the Zavada et al. '370 patent provides more in-depth support regarding the use of PCR primers. [Again, the instant application is a continuation of the Zavada et al. '370 patent, and has the same specification.]

For example, the Zavada et al. '370 patent states at col. 3, lines 33-39:

Fragments of the isolated nucleic acids of the invention, can also be used as PCR primers to amplify segments of MN genes, and may be useful in identifying mutations in MN genes. Typically, said PCR primers are oligonucleotides, preferably at least 16 nucleotides, but they may be considerably longer. Exemplary primers may be from about 16 nucleotides to about 50 nucleotides, preferably from about 19 nucleotides to about 45 nucleotides.

[Emphasis added.]

Further, the Zavada et al. '370 patent states at col. 33, line 30 to col. 34, line 1:

Nucleic acid probes of this invention can be used to detect MN DNA and/or RNA, and thus can be used to test for the presence or absence of MN genes, and amplification(s),

mutation(s) or genetic rearrangements of MN genes in the cells of a patient. For example, overexpression of an MN gene may be detected by Northern blotting and RNase protection analysis using probes of this invention. . . . Southern blotting could also be used with the probes of this invention to detect amplifications or deletions of MN genes. . . . Said probes can also be used to identify MN proteins and/or polypeptides as well as homologs or near homologs thereto by their hybridization to various mRNAs transcribed from MN genes in different tissues.

Probes of this invention thus can be useful diagnostically/ prognostically. Said probes can be embodied in test kits, preferably with appropriate means to enable said probes when hybridized to an appropriate MN gene or MN mRNA target to be visualized. Such samples include tissue specimens including smears, body fluids and tissue and cell extracts.

PCR Assays. To detect relatively large genetic rearrangements, hybridization tests can be used. To detect relatively small genetic rearrangements, as, for example, small deletions or amplifications, or point mutations, the polymerase chain reaction (PCR) would preferably be used. [U.S. Patent Nos. 4,800,159; 4,683,195; 4,683,202; and Chapter 14 of Sambrook et al., *Molecular Cloning: A Laboratory Manual, supra*]

An exemplary assay would use cellular DNA from normal and cancerous cells, which DNA would be isolated and amplified employing appropriate PCR primers.

[Emphasis added.]

Further, for example, the Zavada et al. '370 patent states at column 14, lines 33-37:

Example 13 details further research on MN gene expression wherein MN antigen, as detected by immunohistochemical staining, was found to be prevalent in tumor cells of a number of cancers, including cervical, bladder, head and neck, and renal cell carcinomas among others.

[Emphasis added.] The '370 patent notes at column 57, lines 7-8: "One hundred percent (4 of 4) of the renal cell carcinomas were MN positive."

Zavada et al. U.S. Patents and Applications Provide MN cDNA in Figure 1 and as SEQ ID NO. 1 in Sequence Listings

Applicants respectfully emphasize that all the Zavada et al., U.S. patents and applications show the MN cDNA sequence in Figure 1, which MN cDNA is SEQ ID NO: 1 of the Sequence Listing. Only in the Zavada et al. '676 patent (filed Oct. 21, 1992) is a partial MN cDNA sequence provided. That partial MN cDNA is missing the first about 100 nucleotides that encode the putative signal peptide.

All the other Zavada et al., U.S. patents and applications from which the instant application claims priority show the full-length MN cDNA sequence of 1522 base pairs (bp). The Zavada et al. '370 (filed June 7, 1995), of which the instant

application is a continuation, shows also the full genomic sequence of the MN gene of 10,898 bp, which is shown in Figure 15 and is also provided physically in the A4a, XE1 and XE3 plasmids deposited at the American Type Culture Collection and to which claim 47 of the instant application refers.

Applicants respectfully submit that any one of skill in the art given the MN cDNA of the Zavada et al. patents and applications could design a variety of primers to amplify segments of the MN cDNA. As indicated in the accompanying Appendix 1 claim chart, SEQ ID NO: 2 of the McKiernan et al. '098 patent is NOT such a primer. That wrong McKiernan et al. primer is a 17 nucleotide primer reading 5'-AAAGGCGCTGAGGTGAA-3' that should be a 20 nucleotide primer reading 5'-AAAGGCGGGTGCTGAGGTGAA-3'. The missing GGT is underlined.²

The McKiernan et al. '098 primer SEQ ID NO: 2 would not specifically hybridize under the McKiernan et al. experimental

-
2. McKiernan et al. are mistaken and appear confused about the nature of the MN cDNA sequence. The McKiernan et al. '098 patent at col. 1, lines 64-67 states that "[t]he availability of the complete cDNA sequence for the MN gene product (10) allowed the design of specific PCR primers that amplify a portion of the MN cDNA in a reverse transcriptase-PCR (RT-PCR) assay." They cite to Reference 10 for the complete cDNA sequence. However, that reference -- Der and Stanbridge, Cell, 26: 429 (1981) has absolutely nothing to do with the MN gene or protein, and certainly does not provide the MN cDNA sequence.

conditions to the MN cDNA and therefore would not be effective in amplifying a 386 base pair (bp) fragment of the MN cDNA. When the SEQ ID NO: 2 primer of the McKiernan et al. '098 patent is compared to the MN cDNA, only a 92.9% similarity in 14 bp overlap with MN cDNA is found. That means that the primer is not correct and would provide no RT-PCR product under the experimental conditions of the McKiernan et al. '098 patent. The calculated annealing temperature of the primer is 48°C using Oligo software or 52°C using the formula $T = 4(G+C) + 2(A + T)$, whereas the RT-PCR was performed at 57°C. That means the RT-PCR could not work performed with the SEQ ID NO: 2 primer under the McKiernan et al. experimental conditions.

McKiernan et al. also provide the wrong molecular weight for the MN protein as 51 kd at col. 7, lines 49-51 of the '098 patent. The correct molecular weight for the MN protein is p54/58N as stated in the Zavada et al. '676 patent [Exhibit 2] at col. 9, lines 53-55.

However, one of skill in the art given the MN cDNA sequence that is SEQ ID NO: 1 and shown in Figure 1 of the Zavada et al. U.S. patents and applications would be able to find correct primers to amplify fragments of the MN cDNA for diagnostic/prognostic assay.

Zavada et al. U.S. Patents and Applications and Instant Specification Meet the Written Description Requirement for the Claimed Invention

Applicants respectfully emphasize in regard to "the written description requirement" that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re re Myers, 161 USPQ 668, 671 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ 2nd 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

Applicants respectfully point out that it is not necessary to cite "the exact language", i.e. *ipsis verbis*, in the Specification to support claimed subject matter. ["It is not necessary that the claimed subject matter be described in *ipsis verbis* to satisfy the written description requirement of 35 U.S.C. 112." Nelson v. Bowler, 1 USPQ2d 2076, 2078 (Bd. Pat. App. & Interf. 1986).] The PTO Board of Patent Appeals and Interferences stated in Ex parte Soreson, 3 USPQ2d 1462 (Bd. Pat. App. & Interf. 1987) at page 1463:

[W]e are mindful that appellant's specification need not describe the claimed invention in *ipsis verbis* to comply with the

written description requirement. . . . The test is whether the originally filed specification disclosure *reasonably* conveys to a person having ordinary skill that applicant had possession of the subject matter later claimed. . . .

[Emphasis in original.] [See also, Fujikawa v. Wattanasin, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996) and In re Alton, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).]

Applicants respectfully submit that the Zavada et al. '676 priority application (filed Oct. 21, 1992) reasonably conveys to one of skill in the art that Applicants had possession of the claimed methods at the Oct. 21, 1992 priority date.

RT-PCR Conventional in 1992

At least in 1992, a standard method for the detection and quantification of mRNA is the combined use of reverse transcriptase (RT) and the polymerase chain reaction (PCR) -- RT-PCR. [See Larrick, J.W., Trends Biotechnol., 10: 146-152 (1992); Kawasaki, E.S., PCR Protocols: A Guide to Methods and Applications (eds. Innis, M.A. et al.) Academic Press, San Diego, CA (1990).]

Exemplary articles that provide further evidence of the conventionality of RT-PCR in 1992 include:

- Dooley et al., J. Neuroscience Res., 33: 60-67 (1992);

- Mueller et al., Infection, 20(5): 249-252 (1992);
- Wu et al., Jpn. J. Med. Sci. Biol., 45: 165-174 (1992);
and
- Yuki et al., J. Med. Virol., 37: 237-240 (1992).

Those representative articles are enclosed as Exhibits 4 to 7, respectively.

Enhanced RT-PCR Assay (i.e. Southern Blot Detection of the Amplified Band)

The McKiernan et al. '098 patent (at column 2, lines 57-58) refers to "The enhanced RT-PCR assay" as "(i.e. Southern blot detection of the amplified band)." The Background of the McKiernan et al. '098 patent states (at column 1, lines 29-38):

Increasingly, tumor detection methods that involve DNA- and RNA-based assays of patient specimens are being used (2,3,4). With the use of polymerase chain reaction (PCR) technology to amplify unique genetic sequences which are markers for malignancy, these assays can now detect small numbers of cancer cells in patient blood specimens (5,6).

[Emphasis added.] The citations in that quote are:

2. Wu et al., Detection of **micrometastasis in breast cancer by the polymerase chain reaction**. Lab. Invest., 62: 109A, 1990.
3. Van Dongen et al., Squamous cell carcinoma-associated antigens used in novel strategies for the detection and

treatment of minimal residual head and neck cancer. Anticancer Res., 16: 2409-2413, 1996.

4. Stevens et al., Detection of **tyrosinase mRNA from the blood of melanoma patients**. Cancer Epidermiol., Biomarkers & Prev., 5: 293-296, 1996
5. Miller et al., Detection of minimal residual disease in acute promyelocytic leukemia by a **reverse transcriptase polymerase chain reaction assay** for the PML/RAR- α fusion mRNA. Blood, 82: 1689, 1993.
6. Katz et al., Molecular staging of prostate cancer with the use of **an enhanced reverse transcriptase-PCR assay**. Urology, 43: 765-775, 1994.
7. Burchill et al., Detection of **epithelial cancer cells in peripheral blood by reverse transcriptase-polymerase chain reaction**. Br J. Cancer, 71: 278-281, 1995.

[Emphasis in bold added.]

The McKiernan et al. '098 patent as shown above indicates that enhanced RT-PCR is RT-PCR with Southern blotting, and that RT-PCR. The above citations show that enhanced RT-PCR had been well-known in the art years before the '098 patent's priority date of April 15, 1997. The McKiernan et al. '098 patent states (at column 10, lines 36-39): "When enhanced sensitivity of MN detection was desired (e.g., for peripheral blood samples), Southern blotting of PCR-amplified fragments was

performed using conventional methods (23)." [Citation (23) is to Sambrook et al. *Molecular Cloning: A laboratory manual*, 2d Ed., Cold Spring Harbor Laboratory Press, Salem, Mass (1989).]

The above-cited articles, particularly articles 5-7, show that one of skill in the art only needs to have a blood sample from a person suspected of having cancer and primers from the cDNA of a gene whose expression is known to be associated with the presence of such a cancer, and RT-PCR or enhanced RT-PCR could be used to see if that gene's mRNA extracted from nucleated cells from the blood sample is present at an abnormal level, to detect such a cancer in said person. The Zavada et al. '676 patent (filed on October 21, 1992), as detailed above, provides the required information -- MN gene's expression associated with a variety of cancers including kidney cancer, MN's cDNA sequence, PCR primers, and the fact that PCR-based assays can be used with body fluid samples, such as, blood.

Any one of skill in the art could synthesize a couple of appropriate primers from the cDNA of SEQ ID NO: 1 of the Zavada et al. '676 patent shown in Figure 1A-1B (Exhibit 2) and use RT-PCR or enhanced RT-PCR to detect the presence of amplified MN cDNA as diagnostic for a cancer associated with the abnormal expression of the MN gene.

Clear Cell Renal Carcinoma is Most Common Form of Renal Carcinoma

The McKiernan et al. '098 patent at column 12, lines 31-34 states that clear cell renal carcinoma (RCC) is "the most common form of renal cancer". The National Cancer Institute (NCI) Kidney Cancer Treatment Web Page in July 2001 [<http://web.ncifcrf.gov/research/kidney/path.html>] points out under the heading Pathology of Kidney Cancer: "The current classification of renal cell carcinomas includes: 1) clear cell (origin from proximal tubule; 70-75% of renal tumors). . . ." An alternative name for clear cell carcinoma is "conventional renal cell carcinoma." [Tickoo et al., Am. J. Surg. Pathol., 24(9): 1247-56 (Sept. 2000.)]

The question then is: What could possibly be patentable about a claim to diagnosing clear cell renal carcinoma, over claims to diagnosing renal carcinoma? Applicants respectfully submit that there is nothing patentable in the use of the term "clear cell" to modify "renal carcinoma" especially since most renal carcinomas are clear cell renal carcinomas.

Zavada et al., U.S. Patent No. 6,027,887 Claims Nucleic Acid Based Assays Using Blood Samples

Applicants respectfully point out that Zavada et al., U.S. Patent No. 6,027,887 (hereinafter cited as "the Zavada et

al. '887 patent") (filed January 24, 1997; issued February 22, 2000) claims priority from the same applications/patents as the instant application, but unlike the instant application is a continuation-in-part rather than a continuation of the parent applications filed on June 7, 1995. A copy of the Zavada et al. '887 patent is enclosed as Exhibit 8.

The Zavada et al. '887 patent has 10 claims to methods of screening for preneoplastic/neoplastic disease using a nucleic acid based assay comprising

(a) determining whether abnormal MN gene expression is present in a vertebrate; and

(b) if abnormal MN gene expression is determined to be present in said vertebrate, determining that said vertebrate has a significant risk of having preneoplastic/neoplastic disease;

.

[Claim 1 of the Zavada et al. '887 patent; emphasis added.] Claim 3 of the Zavada et al. '887 patent indicates that the "vertebrate" of Claim 1 is "human."

Claim 5 of the Zavada et al. '887 patent reads:

5. The method according to claim 1 wherein said preneoplastic/neoplastic disease is selected from the group consisting of mammary, bladder, renal, prostate, ovarian, cervical, endometrial, uterine, vaginal, vulval, lung, skin, thyroid, duodenal, jejunal, ileal, colon, rectal, liver, pancreatic, testicular, brain, head and neck

and mesodermal preneoplastic/neoplastic diseases, wherein abnormal MN gene expression is determined to be present if the level of MN gene expression and/or the cellular location of said MN gene expression is or are not normal.

[Emphasis added.]

Claims 9 and 10 of the Zavada et al. '887 patent reads:

9. The method according to claim 8 wherein said sample is selected from the group consisting of tissue sections, tissue extracts, tissue smears, whole cells, cell lysates, exfoliated cells, cell extracts, and body fluids.

10. The method according to claim 9 wherein said body fluids are selected from the group consisting of blood, serum, plasma, urine, semen, breast exudate, saliva, sputum, tears, mucous, fecal suspensions, gastric secretions, bile, lymph, cytosols, ascites, pleural effusions, amniotic fluid, bladder washes, bronchioalveolar lavages and cerebrospinal fluid.

[Emphasis added.]

Applicants respectfully note that support for the above claims of the Zavada et al. '887 patent, as detailed above, can be found in all the Zavada et al. priority applications back to October 21, 1992 for U.S. Serial No. 07/964,589, issued as U.S. Patent No. 5,387,676 on February 7, 1995. McKiernan et al. had all the Zavada et al. information and apparently access to clinical samples from kidney cancer patients. All that McKiernan et al. did was to provide clinical evidence that an aspect of the

Zavada et al. invention, that had been constructively reduced to practice about five years earlier, worked for the most common form of renal carcinoma -- clear cell renal carcinoma -- using a well-known, conventional form of a nucleic based assay -- RT-PCR -- with or without the standard technique of Southern blotting.

35 U.S.C. 135(b)

Applicants respectfully point out that in accordance with 35 U.S.C. 135(b) that claims 38-41 and 43-45 of the instant application as herein presented are "the same as, or for the same or substantially the same subject matter" as claims 1-6 of the McKiernan et al. '098 patent.

Further, Applicants respectfully point out that Claims 1, 3, 4, 5, 8, 9 and 10 of Zavada et al., U.S. Patent Patent No. 6,027,887 ("the Zavada et al. '887 patent") (filed Jan. 24, 1997; issued Feb. 22, 2000) are "the same as, or for the same or substantially the same subject matter as" [35 U.S.C. 135(b)] as are claims 1-6 of the McKiernan et al. '098 patent. The Zavada et al. '887 patent is enclosed as Exhibit 8.

The Zavada et al. '887 patent claims priority from the same Zavada et al. patents/applications as the instant application; however the Zavada et al. '887 patent is a continuation-in-part of the parent applications/patents, whereas

the instant application is a continuation of said parent applications/patents.

CONCLUSION

Applicants most respectfully but earnestly request that an interference be declared between the instant application and the McKiernan et al. '098 patent, wherein the Applicants are declared the senior party. For the reasons detailed above, Applicants respectfully conclude that the pending claims of the instant application are only patentable to the discoverers of the MN gene and protein, who also discovered MN's oncogenic nature and diagnostic/prognostic methods including PCR-based assays using samples which include human body fluids, such as blood, to detect precancerous and cancerous conditions of many different tissues and organs, including renal cell carcinoma (RCC).

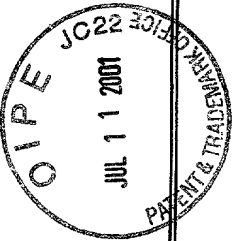
If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the instant application and/or the declaration of the requested interference,

the Examiner is invited to telephone the undersigned Attorney for
the Applicants at 415-981-2034.

Respectfully submitted,


Leona L. Lauder
Attorney for Applicants

Dated: July 11, 2001



McKiernan et al., U.S. Patent No. 6,087,098 (filed April 15, 1997)	Zavada et al., U.S. Patent No. 5,387,676 (filed October 21, 1992) Great-Grand-Parent Application	Zavada et al., U.S. Patent No. 6,204,370 (filed June 7, 1995) Parent Application With Same Specification as Present Application
1. A method for diagnosing a clear cell renal carcinoma	col. 3, lines 18-36, particularly lines 29-30 and 33-34 col. 17, line 7 to col. 18, line 34, particularly, col. 18, lines 20-22 and lines 31-34	col. 4, lines 35-48, particularly lines 46-47 col. 35, lines 12-48 col. 57, lines 7-8 col. 57, lines 25-50 (Table 3)
a human subject	col. 2, lines 21-33 col. 2, lines 42-50 col. 3, lines 7-13 col. 8, line 21 to col. 9, line 43 col. 10, lines 45-60	col. 1, lines 29-30 col. 2, lines 17-32 col. 3, lines 55-66 col. 4, lines 20-31 col. 10, lines 63 - col. 11, line 3 col. 12, lines 55-58 col. 14, lines 29-38 col. 34, lines 16-19
(a) obtaining mRNA from a sample	col. 2, lines 20-36, particularly lines 30-32 col. 5, lines 13-16 col. 8, lines 22-27 col. 11, lines 41-49 col. 17, lines 3-29 col. 35, line 58 to col. 36, line 21 [Example 12]	col. 2, lines 17-32, particularly lines 27-28 col. 3, lines 26-31 col. 10, lines 34-39 col. 15, lines 41-52 col. 16, lines 28-50 col. 18, lines 55-60 col. 33, lines 30-57 col. 53, lines 19-49 [Example 11]

McKiernan et al., U.S. Patent No. 6,087,098 (filed April 15, 1997)	Zavada et al., U.S. Patent No. 5,387,676 (filed October 21, 1992) Great-Great Grand-Parent Application	Zavada et al., U.S. Patent No. 6,204,370 (filed June 7, 1995) Parent Application With Same Specification as Present Application
of the subject's peripheral blood	col. 17, lines 24-29 and lines 44-60 col. 26, lines 5-10	col. 33, lines 52-57 and col. 34, lines 58 to col. 35, line 6
(b) preparing cDNA from the mRNA of step (a)	col. 11, lines 41-49	col. 15, lines 41-52
(c) amplifying DNA encoding MN present in the cDNA prepared in step (b); and	col. 2, lines 20-36 col. 44, lines 40-49 [Claim 8]	col. 2, lines 17-32 col. 3, lines 33-39 col. 16, lines 28-50 col. 27, line 41 to col. 28, line 2 col. 33, line 58 to col. 34, line 13 col. 127, lines 18-20 [Claim 2]
(d) detecting the presence of any resulting amplified DNA	col. 2, lines 20-36 col. 5, lines 13-17 col. 11, lines 41-49 col. 17, lines 3-29	col. 2, lines 17-32 col. 3, lines 26-35 col. 15, lines 40-52 col. 16, lines 28-50 col. 33, line 30 to col. 34, line 13
the presence of such amplified DNA being diagnostic for clear cell renal carcinoma	col. 3, lines 18-36 col. 17, line 67 to col. 18, line 34	col. 4, lines 35-48 col. 35, lines 12-48 col. 57, lines 7-8 col. 57, lines 25-50 (Table 3)
2. The method of claim 1, wherein in step (c) amplification of DNA encoding MN is effected by a polymerase chain reaction	col. 2, lines 20-36 col. 44, lines 40-49 [Claim 8]	col. 2, lines 17-32 col. 3, lines 33-39 col. 16, lines 28-50 col. 27, line 41 to col. 28, line 2

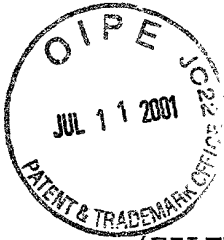
McKiernan et al., U.S. Patent No. 6,087,098 (filed April 15, 1997)	Zavada et al., U.S. Patent No. 5,387,676 (filed October 21, 1992) Great-Grand-Parent Application	Zavada et al., U.S. Patent No. 6,204,370 (filed June 7, 1995) Parent Application With Same Specification as Present Application
utilizing at least two oligonucleotide primers.		col. 33, line 58 to col. 34, line 13 col. 127, lines 18-20 [Claim 2] and lines 47-48 [Claim 11]
3. The method of claim 2, wherein each of the primers is capable of specifically hybridizing with DNA encoding MN.	col. 2, lines 20-36	col. 2, lines 17-32 col. 11, lines 54-61 [Figure 16] col. 16, lines 28-50 col. 17, lines 3-7 col. 17, line 4 to col. 28, line 2 col. 33, line 58 to col. 34, line 13 col. 127, lines 18-20 [Claim 2] and lines 47-48 [Claim 11]
4. The method of claim 3, wherein the primers comprise oligonucleotides having the sequence 5'-GGGACAAAGAAGGGGATGAC-3' (SEQ ID NO: 1)	Figure 1A-1B and Sequence Listing -- SEQ ID NO: 1 -- nucleotide 281 to nucleotide 300	Figure 1A-1B and Sequence Listing -- SEQ ID NO: 1 -- nucleotide 404 to nucleotide 423
and 5'AAAGGCGCTGAGGTGAA-31 (SEQ ID NO: 2).	There is no such MN cDNA sequence as SEQ ID NO: 2 of the McKiernan et al. '098 patent. A primer having the nucleotide sequence of SEQ ID NO: 2 would not work to amplify a 386 bp MN cDNA sequence. No product would result when used with the	As indicated to the left under Zavada et al., U.S. Patent No. 5,387,676 (filed Oct. 21, 1992), SEQ ID NO: 2 of the McKiernan et al. '098 patent would not function as a primer to amplify a 386 bp MN cDNA fragment.

McKiernan et al., U.S. Patent No. 6,087,098 (filed April 15, 1997)	Zavada et al., U.S. Patent No. 5,387,676 (filed October 21, 1992) Great-Great Grand-Parent Application	Zavada et al., U.S. Patent No. 6,204,370 (filed June 7, 1995) Parent Application With Same Specification as Present Application
	<p>other McKiernan et al. primer.</p> <p>The correct primer to amplify said 386 bp MN cDNA sequence would be found to be complementary to nucleotide 647 to nucleotide 666 of Figure 1A-1B which shows SEQ ID NO: 1, which is the MN cDNA sequence, and is contained also in the Zavada et al. Sequence Listing.</p>	<p>Many primers can be designed by one of skill in the art using Figure 1A-1B of the Zavada et al. patents and applications to amplify a variety of MN cDNA fragments. Figure 1A-1B of Zavada et al., U.S. Patent No. 6,204,370 (filed June 7, 1995) shows the full-length MN cDNA. The correct primer to amplify a 386 bp MN cDNA fragment with the primer of SEQ ID NO: 1 of the McKiernan et al. '098 patent would be the primer complementary to nucleotides 789 to 770 of Figure 1A-1B or of SEQ ID NO: 1 of the Zavada et al. '370 patent.</p>
5. The method of claim 1, wherein the presence of any amplified DNA in step (d) is detected using a labeled oligonucleotide probe which specifically hybridizes with the amplified DNA.	col. 2, lines 20-36 col. 17, lines 3-29, particularly lines 24-27 col. 36, lines 3-18	col. 2, lines 18-32 col. 3, lines 33-39 col. 33, line 30 to col. 34, line 13, particularly, col. 33, lines 52-55
6. The method of claim 5, wherein the labeled probe is radiolabeled with ³² P.	col. 20, lines 18-22	col. 17, lines 42-46 col. 18, lines 66-67 col. 19, lines 19-23

APPENDIX 2

Paragraph on page 1, lines 2-14 has been amended as follows:

This application is a continuation of ~~allowed~~ U.S. Serial No. 08/485,049 (filed June 7, 1995), which issued as U.S. Patent 6,204,370 on March 20, 2001, which is a continuation-in-part of now pending U.S. Serial No. 08/260,190 (filed June 15, 1994), which, in turn, is a continuation-in-part of U.S. Serial No. 08/177,093 (filed December 30, 1993), which issued as U.S. Patent 6,051,226 on April 18, 2000, which is, in turn, a continuation-in-part of U.S. Serial No. 07/964,589 (filed October 21, 1992), which issued as U.S. Patent No. 5,387,676 on February 7, 1995. This application declares priority under 35 USC § 120 from those U.S. applications, and also under 35 USC § 119 from the now pending Czechoslovakian patent application PV-709-92 (filed March 11, 1992).



APPENDIX 3

PENDING CLAIMS FOR U.S. SERIAL NO. 09/772,719
(FILED JANUARY 30, 2001) ENTITLED "MN GENE AND PROTEIN"

38. A method for diagnosing renal carcinoma in a human subject which comprises:

- (a) obtaining mRNA from a sample of the subject's blood;
- (b) preparing cDNA from the mRNA from step (a);
- (c) amplifying DNA encoding MN present in the cDNA prepared in step (b); and
- (d) detecting the presence of any resulting amplified DNA, the presence of such amplified DNA being diagnostic for renal carcinoma.

39. The method of claim 38, wherein in step (c) amplification of DNA encoding MN is effected by a polymerase chain reaction utilizing at least two oligonucleotide primers.

40. The method of claim 39, wherein each of the primers is capable of specifically hybridizing with DNA encoding MN.

41. The method of claim 39, wherein the primers comprise oligonucleotides that are effective to amplify a segment of the MN cDNA.

42. The method of claim 41 wherein said MN cDNA has the nucleotide sequence of SEQ ID NO: 1.

43. The method of claim 42 wherein one of said primers comprises the nucleotide sequence of nucleotide 404 to nucleotide 423 of Figure 1A-1B and of SEQ ID NO: 1, and the other primer is complementary to nucleotides 789 to 770 of Figure 1A-1B and of SEQ ID NO: 1.

44. The method of claim 38, wherein the presence of any amplified DNA in step (d) is detected using a labeled MN nucleic acid probe which specifically hybridizes with MN nucleic acids encoding a MN protein or MN polypeptide, which MN protein or MN polypeptide has an amino acid sequence of or from SEQ ID NO: 2.

45. The method of claim 44, wherein the labeled probe is radiolabeled.

46. The method of claim 39 wherein each of said primers is an isolated and purified MN nucleic acid, which has a length of from 16 nucleotides to 50 nucleotides, and comprises a nucleotide sequence which is selected from the group consisting of: nucleotide sequences that specifically hybridize to SEQ ID NO: 1 or to the complement of SEQ ID NO: 1; and

wherein an appropriate pair of primers is selected for effective amplification.

47. The method of claim 46 wherein said nucleotide sequence specifically hybridizes to a MN nucleotide sequence contained in any of the plasmids A4a, XE1 and XE3, which were deposited at the American Type Culture Collection in the United States of America under the respective ATCC Nos. 97199, 97200 and 97198.

48. A method of screening for preneoplastic/neoplastic disease associated with abnormal MN gene expression comprising:

(a) determining whether abnormal MN gene expression is present in a vertebrate using a nucleic acid based assay on a sample from said vertebrate; and

(b) if abnormal MN gene expression is determined to be present in said vertebrate, determining that said vertebrate has a significant risk of having preneoplastic/neoplastic disease;

wherein said MN gene encodes an MN protein that is encoded by a nucleic acid having a nucleotide sequence selected from the group consisting of:

(a) SEQ ID NO: 1;

(b) nucleotide sequences that hybridize under stringent conditions to complement of SEQ ID NO: 1; and

(c) nucleotide sequences that differ from SEQ ID NO: 1 or from the nucleotide sequences of (b) in codon sequence due to the degeneracy of the genetic code.

49. The method of claim 48 wherein said MN protein is encoded by SEQ ID NO: 1.

50. The method of claim 49 wherein said vertebrate is a mammal.

51. The method of claim 49 wherein said vertebrate is a human.

52. The method of claim 51 wherein said nucleic acid based assay is a polymerase chain reaction based assay.

53. The method of claim 51 wherein detecting abnormal MN gene expression comprises:

(a) obtaining mRNA from said sample from said human;

and

(b) detecting the presence of mRNA that is complementary to MN cDNA in the mRNA obtained from step (b), or quantitating any mRNA that is complementary to MN cDNA in the mRNA obtained from step (b);

wherein the presence of mRNA complementary to MN cDNA in said mRNA obtained in step (a), or an abnormal level of mRNA complementary to MN cDNA in said mRNA obtained in step (a), indicates the presence of preneoplastic/neoplastic disease in said human.

54. The method of claim 51 wherein abnormal MN gene expression is detected by:

(a) obtaining mRNA from a sample from said human;

(b) preparing cDNA from the mRNA from step (a);

(c) amplifying any DNA encoding a MN protein or a MN polypeptide that is present in the cDNA prepared in step (b); and

(d) detecting the presence of any resulting amplified DNA, or quantitating any resulting amplified DNA, wherein the presence of such amplified DNA or an abnormal level of said amplified DNA indicates the presence of preneoplastic/neoplastic disease in said human.

55. The method of claim 54, wherein the step (c) amplification of DNA is effected by a polymerase chain reaction utilizing at least two oligonucleotide primers.

56. The method of claim 55 wherein each of the primers is capable of specifically hybridizing with DNA that encodes MN protein.

57. The method of claim 56 wherein said DNA that encodes MN protein has the nucleotide sequence of SEQ ID NO: 1.

58. The method of claim 57 wherein one of said primers has the nucleotide sequence of nucleotide 404 to nucleotide 423 of Figure 1A-1B or of SEQ ID NO: 1, and the other primer is complementary to nucleotide 789 to nucleotide 770 of Figure 1A-1B or of SEQ ID NO: 1.

59. The method of claim 54, wherein the presence of any amplified DNA in step (d) is detected using a labeled MN nucleic acid probe which specifically hybridizes with any amplified MN DNA.

60. The method of claim 59, wherein the labeled probe is radiolabeled.

61. The method of claim 60 wherein the labeled probe is radiolabeled with ^{32}P .

62. The method of claim 53 wherein said sample is selected from the group consisting of tissue sections, tissue extracts, tissue smears, whole cells, cell lysates, exfoliated cells, cell extracts, and body fluids.

63. The method according to claim 62 wherein said body fluid is selected from the group consisting of blood, serum, plasma, urine, semen, breast exudate, saliva, sputum, tears, mucous, fecal suspensions, gastric secretions, bile, lymph, cytosols, ascites, pleural effusions, amniotic fluid, bladder washes, bronchioalveolar lavages and cerebrospinal fluid.

64. The method according to claim 63 wherein said body fluid is selected from the group consisting of blood, serum and plasma.

65. The method according to claim 64 wherein said body fluid is blood.

66. The method of claim 54 wherein said preneoplastic/neoplastic disease associated with abnormal MN gene expression is selected from the group consisting of mammary, urinary tract, bladder, kidney, ovarian, uterine, cervical, endometrial, squamous cell, adenosquamous cell, vaginal, vulval, prostate, liver, lung, skin, thyroid, pancreatic, testicular, brain, head and neck, mesodermal, sarcomal, stomach, spleen, gastrointestinal, esophageal, and colon preneoplastic/neoplastic diseases.

67. The method of claim 66 wherein said neoplastic disease is renal carcinoma.